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Review Paper
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Nutrition, brain function and cognitive performance[☆]

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Abstract

Military interest in the effects of nutritional factors on cognitive function has stimulated considerable research on a variety of food constituents. This paper will review the research on the amino acids tryptophan and tyrosine, caffeine and carbohydrate. It will focus on research that addresses the potential utility of these compounds in military applications, particularly the acute, as opposed to chronic, effects of these substances on cognitive functions such as alertness, vigilance and resistance to stress. Caffeine, the most intensively studied food constituent, has unequivocal beneficial effects on vigilance, and in sleep deprived individuals it enhances other cognitive functions as well. Tryptophan, although it clearly has sedative-like properties, has not been extensively studied by military laboratories for use as a hypnotic, due to safety concerns. Tyrosine has been examined in animal models and human studies, and appears to prevent the substantial decline in various aspects of cognitive performance and mood associated with many kinds of acute stress. Carbohydrate supplementation appears to enhance cognitive performance in soldiers engaged in sustained, intense physical activities that expend high levels of energy.

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Keywords: Nutrition; Tryptophan; Caffeine; Protein; Carbohydrate; Cognitive; Mood; Stress

Introduction

The scientific examination of relationships between nutrition and behavior is a relatively new area of study, although there are many popular beliefs about the behavioral effects of foods. Some of these common sense beliefs about food and behavior have proven to be true, like the anecdotal observation that sleepiness often ensues after consumption of a large meal (Smith, Leekam, Ralph, & McNeill, 1988). However, others are myths, such as the hypothesis that sugar causes hyperactivity, which has been refuted by a number of well-designed studies (Bellisle et al., 1998; Kanarek, 1994). This paper will review the effects that a number of food constituents have on human behavior, the biochemical basis for such effects and the manner in which these foods may affect military performance.

Recent research has shown that relationships between nutrition and behavior can be complex. There can be unanticipated behavioral consequences of changes in the diet, such as the adverse symptoms that can occur in heavy

users of caffeine when it is suddenly withdrawn from their diet (Silverman, Evans, Strain, & Griffiths, 1992). Furthermore, dietary factors may influence the performance of military and civilian personnel engaged in various critical tasks. A number of monographs, relating cognitive function to key military nutrition issues have been published by the Committee of Military Nutrition of the Institute of Medicine. These monographs provide a comprehensive collection of papers addressing a wide range of issues including: undernutrition, unique military nutritional requirements, performance enhancement and nutrition in extreme environments (Carlson-Newberry & Costello, 1997; Committee on Military Nutrition, 1994; Committee on Military Nutrition, Food and Nutrition Board, Institute of Medicine, 1999, 2001; Marriott, 1995).

The biological basis for effects of food constituents on behavior

For many years it was believed that the blood–brain barrier (BBB) protected the central nervous system from most peripheral metabolic events, such as changes in plasma concentrations of various food constituents, hormones or metabolites after meal consumption. Although there is an element of truth to this generalization, there are many

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Table 1
CNS amino acid transport mechanisms

Large neutral	Basic	Acidic
Leucine	Lysine	Glutamate
Phenylalanine	Arginine	Aspartate
Tryptophan	Ornithine	
Tyrosine		
Valine		
Isoleucine		

From Lieberman (1999).

exceptions to the rule. The BBB is actually selectively permeable, allowing a wide variety of biologically relevant substances to enter the brain (Pardridge, 1986). Not only is the BBB permeable to endogenous and exogenous behaviorally active, lipid soluble compounds such as the hormone melatonin (Lieberman, Waldhauser, Garfield, Lynch, & Wurtman, 1984), a number of lipophobic substances can also cross via special transport mechanisms (Pardridge, 1986). One such transport system conveys the large neutral amino acids (LNAAs) into the brain, another transports choline, and still another, the basic amino acids (Table 1). Furthermore, under certain circumstances, some of these nutrients can affect central neurotransmitter synthesis and potentially, behavior (Fernstrom, 1983; Wurtman, Hefti, & Melamed, 1981). Nutrients like choline, tryptophan, tyrosine, phenylalanine, arginine and threonine are all precursors for neurotransmitters or neuromodulators, and their availability may, under certain conditions, influence the levels of specific neurotransmitters (Table 2, Lieberman, 1999).

Assessing the effects of nutritional factors on cognitive function

A wide variety of behavioral tests have been employed to assess the effects of nutritional interventions on

Table 2
Amino acids and their neurotransmitter/neuromodulator products

Amino acid	Product
Tryptophan	Serotonin Melatonin ^a
Tyrosine/phenylalanine	Dopamine Norepinephrine Epinephrine
Histidine	Histamine
Arginine	Nitric oxide
Threonine (etc.)	Glycine

From Lieberman (1999).

^a Melatonin is not believed to be a neurotransmitter but is a behaviorally active metabolite of tryptophan synthesized by the pineal gland. There is evidence that administration of tryptophan increases the release of melatonin in humans (Hajak et al., 1991).

cognitive function (Bellisle et al., 1998; Lieberman, Spring, & Garfield, 1986; Meiselman & Lieberman, 1994). In some experiments a battery of tests that assess a broad range of functions are used. In other studies an investigator will focus on a particular function, such as memory. While this may be an appropriate strategy given the desire to test a particular hypothesis, it may make the results of the study difficult to interpret, since specific effects observed may be secondary to more general cognitive changes. Generally, it is difficult to determine whether the effects of a food constituent are specific to a particular cognitive function or are of a broader, more general nature. In most instances when investigators employ a diverse battery of tests, only a limited number are affected by a particular nutritional treatment. However, this does not establish that the treatment being evaluated only affects those functions. This is because tests that assess various cognitive domains have not been equated with regard to their sensitivity. It is not even clear how to equate tests of different cognitive functions, since unlike biochemical assays; behavioral tests have no physical anchor. Therefore, failure to detect an effect of a nutrient on a particular domain may be the result of lack of sensitivity of the test, not the true absence of an effect. This methodological weakness puts the onus on the investigator who reports negative results to utilize a wide variety of tests within and across modalities, before claiming a certain food constituent has differential effects on particular aspects of cognition. Mood questionnaires can be particularly useful for validating the effects detected by cognitive tests if they measure similar parameters.

It does appear that some nutritional interventions have fairly specific effects on certain cognitive functions. As discussed below, caffeine, at least in rested individuals, appears to be relatively specific, having few effects on higher cognitive functions such as memory and reasoning, but reliable effects on parameters such as vigilance and related mood states such as fatigue and alertness (Amendola, Gabrieli, & Lieberman, 1998; Lieberman, 2001; Smith, 2002). Caffeine's effects appear to generalize to a wide range of behavioral parameters when individuals are sleep deprived (Lieberman et al., 2003; Penetar et al., 1994), indicating that the context in which testing is conducted can be critical (Committee on Military Nutrition, 1994; Meiselman & Lieberman, 1994). Unlike caffeine, tyrosine appears to have little or no effect on rested, unstressed volunteers (Lieberman, Corkin, Spring, Growdon, & Wurtman, 1983). However, when it is administered to sleep deprived and stressed subjects, it affects a broad range of cognitive parameters such as vigilance, memory and mood (Banderet & Lieberman, 1989; Neri et al., 1995; Shurtleff, Thomas, Schrot, Kowalski, & Harford, 1994). Individual differences in response to particular food constituents also make it more difficult to determine whether the substance in question really alters behavior (Meiselman & Lieberman, 1994).

Tryptophan, melatonin and tyrosine

Among the most intensively studied food constituents are two LNAAs, tryptophan and tyrosine. These have been the focus of considerable behavioral inquiry because they are precursors of several important central neurotransmitters (Wurtman et al., 1981). Melatonin, a metabolite of tryptophan, is a hormone produced by the pineal gland. For regulatory purposes it is considered to be a nutritional supplement in the United States and is clearly behaviorally active.

Tryptophan

One of the neurotransmitter precursors that most clearly affects behavior is the LNA tryptophan. Tryptophan, an essential amino acid, found in nearly all protein containing foods, is the precursor of the neurotransmitter serotonin. Serotonin has a variety of functions in the brain, including a role in the regulation of mood state, particularly depression and alertness. Serotonergic neurons also participate in the regulation of pain sensitivity, aggression and food consumption (Lieberman et al., 1983; Young, 1986). Several years ago ingestion of tryptophan supplements were associated with a rare disorder termed Eosinophilia-myalgia syndrome (EMS) (Hertzman et al., 1990). It now appears EMS is caused by a contaminant found in the tryptophan produced by one manufacturer (Belongia et al., 1990). Due to the association of tryptophan and tryptophan-containing supplements with EMS, the US Food and Drug Administration (FDA) withdrew them from the market. Individuals who were taking tryptophan typically used it as a sleep aid, but it was also used as an antidepressant and for premenstrual syndrome. Although tryptophan is not approved for use as a hypnotic in the United States, it clearly has sedative-like effects on humans when it is administered in pure form and in sufficient quantity (Lieberman et al., 1986). Many studies have consistently detected effects of tryptophan on sleepiness, reporting it to be a useful sedative (Hartmann & Elion, 1977), although this is a subject of considerable controversy.

The induction of sleepiness by a drug/nutrient does not demonstrate the substance is a useful sleep aid. Generally, for a compound to be accepted as an efficacious hypnotic, polysomnography must be used to show that it increases sleep time among patients suffering from insomnia. Results of polysomnographic studies in patients with insomnia given tryptophan as a sleep aid are less consistent than studies using more potent hypnotics, such as the benzodiazepines and barbiturates (Spinweber, 1986a). While tryptophan may lack the potency of hypnotic drugs, it may, under certain circumstances, still be useful as a mild sleep aid in military operations.

The use of effective, but short acting hypnotics may provide warfighters the opportunity to sleep when it would otherwise not be possible (Caldwell et al., 1996; Penetar, Belenky, Garrigan, & Redmond, 1989; Storm & Parke, 1987). Hypnotics have been used effectively in military operations, including wartime (Nicholson, 1984; Senechal, 1988). Although tryptophan may have some unique benefits as a hypnotic, little recent military or civilian research on it has been conducted due to the safety issues raised by the EMS debacle. One military study indicated that it might be possible to use tryptophan, like other classic hypnotics, to synchronize circadian rhythms following travel across multiple time zones. In that study, conducted with US Marines, tryptophan administration hastened re-entrainment of circadian rhythms of performance following air deployment from California to Okinawa (Spinweber, 1986b).

One potential benefit of tryptophan as a sleep aid is that it does not appear to impair various aspects of performance including simple and choice reaction time, manipulative dexterity, and visually guided motor performance, either immediately following administration or the next day (Lieberman et al., 1986; Spinweber, 1986b; Thorleifsdottir, Bjornsson, Kjeld, & Kristbjarnarson, 1989). More potent sedatives impair several types of cognitive performance, not only immediately after administration, but also when patients are tested the next day, particularly if the drug in question has a long half-life (Johnson & Chernik, 1982).

Melatonin

Melatonin, a hormone released by the pineal gland, also has hypnotic properties (Lieberman et al., 1984) and is sold in the United States as a nutritional supplement. Melatonin is a metabolite of tryptophan and serotonin. Administration of tryptophan may increase the release of melatonin in humans (Hajak et al., 1991). Melatonin has hypnotic properties even in very low doses (Dollins et al., 1993; Lieberman et al., 1984). At least one military field study has been conducted to explore its possible utility in military operations as a hypnotic and a circadian resynchronizer (Comperatore, Lieberman, Kirby, Adams, & Crowley, 1996). This study indicated that melatonin speeded resynchronization and improved vigilance in an aviation unit transported across multiple time zones. For recent reviews regarding this substance, see Caldwell (2000) and Herxheimer and Petrie (2001).

Tyrosine

The behavioral effects of another amino acid, tyrosine, the precursor of the catecholamines, have also been examined for potential use in military operations. In a comprehensive review of the utility of using food components to enhance military performance, the CMNR concluded that tyrosine was a leading candidate for use

as a cognitive performance enhancer in military operations (Committee on Military Nutrition, 1994).

A series of pre-clinical, animal studies have been conducted with this amino acid. In aggregate, these studies clearly indicate that tyrosine reduces many of the adverse effects of acute stress on cognitive performance in a wide variety of stressful environments. Given this unique potential use, it is not surprising that tyrosine has been the focus of considerable military interest for its cognitive 'anti-stress' effects (Lieberman, 1994). For recent reviews see Lieberman (1999) and Lieberman and Shukitt-Hale (1996).

The physiological basis of tyrosine's beneficial effects on cognitive function is widely attributed to its role as a precursor for the synthesis of norepinephrine (NE) and dopamine. These neurotransmitters play a key role in a variety of stress related-behaviors. Furthermore, NE is critical for modulating the central stress response (Gray, 1982). Many forms of stress cause the release of large amounts of NE in several brain regions, which are critical for the regulation of stress-related behaviors. During acute stress, NE is depleted, and when additional substrate in the form of tyrosine is provided, the release of NE increases (Lehnert, Reinstein, Strowbridge, & Wurtman, 1984; Yeghiayan, Luo, Shukitt-Hale, & Lieberman, 2001). Tyrosine affects the same neurotransmitter systems as the amphetamines and related drugs, which are potent performance-enhancing compounds, although they have many side-effects (Hull & Maher, 1990; Yeghiayan et al., 2001). To date, in a series of animal studies conducted at several laboratories, including our own, it has been shown that the effects of heat, cold, high altitude and psychological stress are all mitigated by administration of tyrosine (Lehnert et al., 1984; Lieberman & Shukitt-Hale, 1996; Rauch & Lieberman, 1990; Shukitt-Hale, Stillman, & Lieberman, 1996; Yeghiayan et al., 2001).

Although it has been difficult to conclusively demonstrate that tyrosine has beneficial effects in humans, in part due to ethical concerns, the preponderance of evidence from our laboratory, as well as several others, suggests that tyrosine has utility as an acute treatment to prevent stress-related declines in cognitive function. Stressors that have been evaluated in human studies include: the psychological stress of military operations (Deijen, Wientjes, Vullingsh, Cloin, & Langefeld, 1999), cold stress (Shurtleff et al., 1994), the combination of cold and high altitude stress (Banderet & Lieberman, 1989), cardiovascular stress designed to simulate space flight (Dollins, Krock, Storm, Wurtman, & Lieberman, 1995) and sustained operations (Neri et al., 1995).

A wide variety of cognitive tasks, symptoms and moods have been shown to be affected by tyrosine administration in acutely stressed volunteers. Banderet and Lieberman (1989) found that vigilance, choice reaction time, pattern recognition, coding and complex behaviors, such as map-compass reading, were all improved by tyrosine administration when volunteers were exposed to the combination of cold and high

altitude (hypoxia). Many of the adverse symptoms associated with these stressors, such as perceived coldness and headache, were reduced by tyrosine administration and many mood states, such as fatigue, confusion and tension improved. Shurtleff et al. (1994) observed that tyrosine had beneficial effects on working memory in the cold. Deijen et al. (1999) found that tyrosine improved memory, tracking and mood in cadets enrolled in a demanding combat training course. To date it has been difficult to demonstrate unequivocal dose-response effects of tyrosine in humans, however, in animal studies clear dose-response relationships have been observed (Yeghiayan et al., 2001). It is difficult to safely and ethically replicate the more definitive animal studies in human volunteers. The high levels of acute stress and high doses of tyrosine employed in the animal studies are difficult to duplicate in humans.

Protein and carbohydrate foods

The scientific literature addressing the effects of macronutrients—protein, carbohydrate and fat, on cognitive function is quite limited (Bellisle et al., 1998; Kanarek, 1997). If clear beneficial or adverse effects of particular macronutrients could be documented, this would be of great interest and utility to the military. Parametric studies to address the cognitive consequences of consuming foods varying in protein, carbohydrate and fat content have not been conducted and many of the published studies in this area appear contradictory. For example, different investigators have reported that carbohydrate or glucose can both enhance and impair cognitive function (Bellisle et al., 1998; Korol & Gold, 1998). Close examination of the results of many of these apparently contradictory studies often reveal substantial methodological differences, and in some cases weaknesses in study design, which account for the divergent findings. Particularly important issues in study design are failure to recognize the importance of differences in total energy supplied between different treatments, and lack of an appropriate placebo or control treatment. Inclusion of true placebo treatments in studies of real foods can, in many instances, be impossible. For example, a placebo for a large dose of a solid carbohydrate food cannot be formulated to be identical in taste and appearance to it. If a placebo food were composed of a non-nutritive substance it would produce gastrointestinal upset, thereby confounding the results. Overall, the confusing and contradictory nature of the scientific literature in this area makes it difficult to provide specific recommendations regarding macronutrient intake as far as cognitive benefits, or adverse effects, are concerned. The consensus of scientific evidence suggests that breakfast meals, especially when provided to children and elderly volunteers, have beneficial effects and that large lunch meals, especially in sedentary adults, are soporific (Bellisle et al., 1998; Kanarek, 1997; Kaplan, Greenwood,

Table 3

Approximate schedule of events during testing of the ERGO® drink carbohydrate beverage

Activity	Times
1. Check in	0445
2. Vigilance monitors placed on subjects	0500
3. Breakfast and treatment 1	0500
4. First mood assessment (POMS)	0515
5. March begin—19.3 km (12 mile)	0545
6. Treatment 2, 3	0700, 0800
7. March end	0900
8. Treatment 4	0915
9. First run—4.8 km (3 mile)	0930
10. Four hour rest	0950
11. Second mood assessment (POMS)	1030
12. Lunch and treatment 5	1115
13. Treatment 6	1320
14. Second run—4.8 km (3 mile)	1350
15. Run 2 end	1415
16. Third mood assessment (POMS)	1445
17. Subjects released	1500

Modified from Lieberman et al. (2002); POMS, profile of mood states.

Winocur, & Wolever, 2001). The precise macronutrient content of such meals does not appear to be critical.

We have found at least one circumstance with important military implications for which there are unequivocal, beneficial behavioral effects of providing supplemental energy, in the form of a carbohydrate beverage (Lieberman, Falco, & Slade, 2002). Recently, we conducted a double-blind, placebo-controlled study with a US Army Special Operations unit designed to assess effects of a specially formulated carbohydrate supplement, the ERGO® drink, on physical and cognitive performance. The beverage was formulated at Natick Labs, the DoD food developer. Unlike

commercial carbohydrate sport drinks, the ERGO® drink was predominately composed of maltodextrin, a complex carbohydrate, in contrast to the simple sugars used in typical commercial products. The military unit we tested was engaged in a training exercise we designed to simulate a typical infantry combat operation. The exercise included marching, running and a live fire rifle marksmanship test and lasted about 10 h (Table 3). During the study we continuously assessed auditory vigilance with custom-designed and constructed ambulatory vigilance monitors (Lieberman & Coffey, 1997, 2000). Regular meals provided during the exercise were not sufficient to meet the energy needs of the study participants. The 143 male volunteers were randomly divided into three groups who received, on six occasions over the test day, either a placebo beverage, a 6 or 12% carbohydrate beverage. These beverages were identical in taste and appearance and provided equal fluid volumes to the volunteers. Using liquid carbohydrate supplementation overcomes the inherent limitation of using solid foods in such studies, because an identical placebo can be formulated. In this situation carbohydrate supplementation not only enhanced physical performance, but also significantly improved vigilance (Fig. 1, Lieberman et al., 2002). The effects of energy/carbohydrate supplementation were robust and dose-related since the moderate (6%) dose of carbohydrate (35 kJ/kg) had effects on vigilance that were intermediate between the placebo condition (0 kJ/kg) and the higher (12%) dose treatment (70 kJ/kg). Positive changes in mood state, specifically increased vigor and decreased confusion among volunteers receiving the ERGO® drink, corroborate the vigilance results. Additional research to extend this work by determining whether other foods have similar effects is necessary.

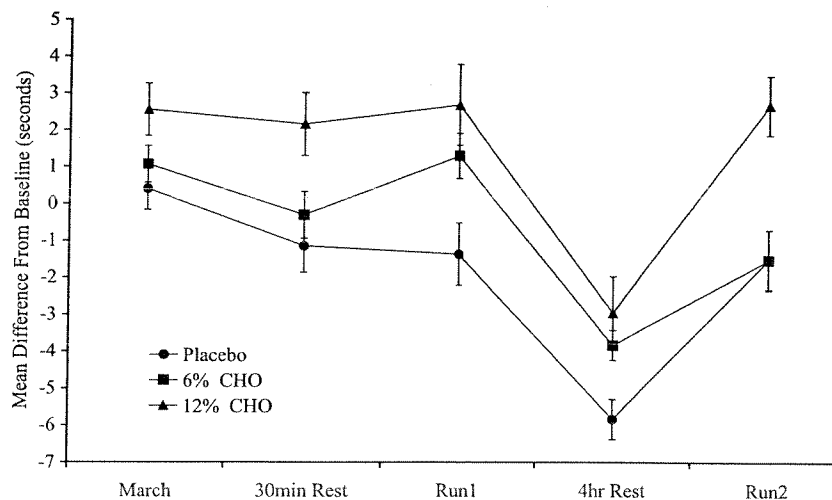


Fig. 1. Vigilance performance of soldiers who received different doses of a carbohydrate beverage or placebo while engaging in various activities. The effects of 6 and 12% carbohydrate beverages and placebo on mean (\pm SEM) auditory vigilance reaction time difference scores (in seconds) over the 10 h of the field study are illustrated. The subjects were tested continuously by an ambulatory monitor they wore on their non-preferred wrist. Their performance was summed over five time periods. Since the values plotted are difference from baseline scores, a higher number on the y-axis indicates improved performance (Lieberman et al., 2002).

Caffeine

Caffeine is a behaviorally active food constituent and drug that is naturally present in many popular foods (Committee on Military Nutrition Research, Food and Nutrition Board, Institute of Medicine, 2001; Lieberman, 2001; Smith, 2002). Caffeine is a methylated xanthine-1,3,7-trimethylxanthine. Foods containing caffeine are consumed by a large part of the world's population. Coffee, tea and colas all contain caffeine and are popular in many countries throughout the world. Many individuals believe that the active component of tea is theophylline. However, caffeine, not theophylline, is the principle xanthine found in tea, although caffeine is metabolized to theophylline *in vivo* (Hirsh, 1984). Although the levels of caffeine in foods vary greatly, coffee typically contains the most caffeine, about 65–110 mg per cup, tea an intermediate amount, about 40–60 mg per cup and cola and some other soft drinks about 40 mg per serving. Detailed information on the sources of caffeine in the diet and their caffeine content can be found in Barone and Roberts (1996) and Lieberman (2001).

The use of caffeine in military operations was recently reviewed by the CMNR who concluded that caffeine, in doses of 100–600 mg, can maintain cognitive performance, especially in situations of sleep deprivation (Committee on Military Nutrition Research, Food and Nutrition Board, Institute of Medicine, 2001). The report was based on research conducted at a number of institutions, including several military laboratories, that demonstrated caffeine consistently improves vigilance in rested volunteers, and has more generalized effects on cognitive performance in sleep deprived individuals (Amendola et al., 1998; Committee on Military Nutrition Research, Food and Nutrition Board, Institute of Medicine, 2001; Lieberman, Wurtman, Emde, & Coviella, 1987; Lieberman, Wurtman, Garfield, Roberts, & Coviella, 1987; Lieberman et al., 2003; Kamimori et al., 2002; Penetar et al., 1994; Smith, Maben, & Brockman, 1994).

Caffeine appears to exert its effects on the brain via modulation of the putative inhibitory neurotransmitter adenosine (Hirsh, 1984; Snyder, Katims, Annau, Bruns, & Daly, 1981). Adenosine, a cyclic nucleotide, can be found in many areas of the brain. Functional adenosine receptors, particularly the A₁ sub-type, are involved in regulation of arousal level. Caffeine, which readily crosses the BBB, blocks the effects of adenosine on brain neurons. Since adenosine is believed to be an endogenous inhibitory neurotransmitter or neuromodulator, caffeine, by reducing its effects, can stimulate brain neurons that have functional adenosine receptors (Hirsh, 1984).

USARIEM investigators have conducted a number of studies (Fine et al., 1994; Johnson & Merullo, 2000; Lieberman et al., 2003; Tharion et al., 1997) of caffeine in both rested and sleep deprived volunteers. This work has utilized caffeine in moderate doses (up to 300 mg), and often focused on vigilance as a critical dependent measure

(Fine et al., 1994; Johnson & Merullo, 2000). The intent of this work was to demonstrate that caffeine had militarily-relevant, beneficial effects on cognitive performance. For example, Fine et al. (1994) conducted a study with a specially developed visual vigilance task designed to have military face validity. The task simulated attending to a radar screen for a sustained period of time (2 h) (Lieberman, Coffey, & Kobrick, 1998). Previously, it had been shown that caffeine, in moderate doses (32–256 mg), had beneficial effects on auditory vigilance in rested civilian volunteers (Clubley, Bye, Henson, Peck, & Riddington, 1979; Lieberman et al., 1987a,b). The study conducted by Fine et al. (1994) demonstrated that a single, moderate dose of caffeine (200 mg), when given to non-sleep deprived military volunteers, significantly improved vigilance for 2 h following administration.

In other studies, the military applicability of caffeine's effects on vigilance were replicated and extended by Johnson and Merullo (2000). They demonstrated, in a series of studies using a marksmanship simulator with non-sleep deprived military volunteers, that 200 mg of caffeine improved target detection speed without adversely affecting rifle-firing accuracy (Fig. 2).

Additional work at USARIEM has evaluated the effects of caffeine during severe operational stress and sleep deprivation (Lieberman et al., 2003; Tharion et al., 1997).

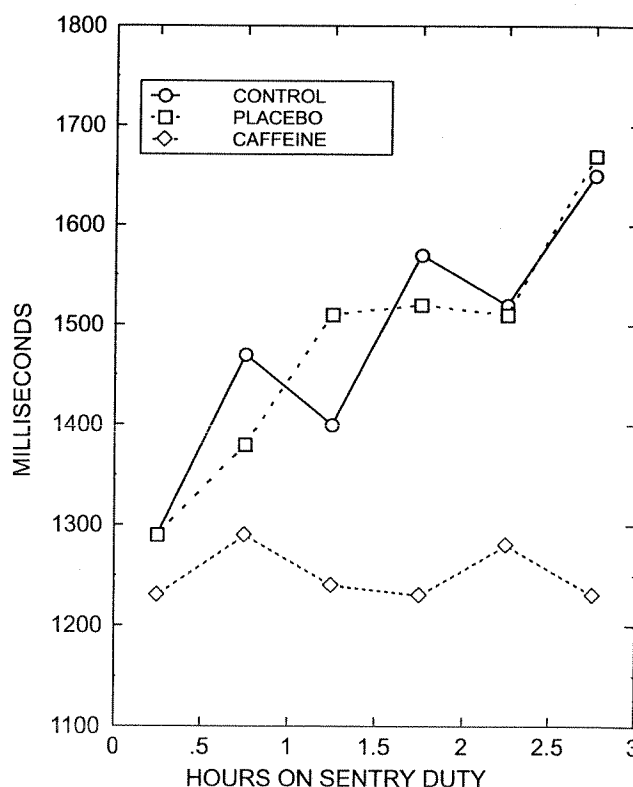


Fig. 2. The effects of 200 mg of caffeine versus either a placebo or a no-treatment (control) condition on target detection response time over three hours of a simulated sentry duty task ($N = 24$) (Johnson & Merullo, 2000).

In a study with US Navy SEAL trainees, a dose-response study of caffeine was conducted during an extraordinarily stressful week of training known as 'Hell Week'. The stress of Hell Week includes: near total sleep deprivation, exposure to cold, continuous, often intense physical activities and extensive psychological stress, and appears to come as close to the extraordinary level of the stress of combat as can be simulated.

For this study, caffeine in doses of 100, 200 and 300 mg, or placebo, was administered to SEAL trainees after 3 days of sleep deprivation and a variety of cognitive tests were administered. Caffeine produced dose-related improvements in visual vigilance, choice reaction time, repeated

acquisition (a test of learning and memory), and reduced self-reported fatigue and sleepiness as shown in Fig. 3. The greatest effects of caffeine were measured 1 h following administration, but significant effects persisted for 8 h. This study demonstrated that even in the most adverse operational circumstances, moderate doses of caffeine had unequivocal, beneficial effects on cognitive performance. Furthermore, it indicated that the optimal dose of caffeine to employ under such conditions was 200 mg, the equivalent to about two cups of coffee (Lieberman et al., 2003).

Recently a caffeine-containing gum has been commercially formulated. Research conducted by the US Army's Walter Reed Laboratory (WRAIR) has demonstrated

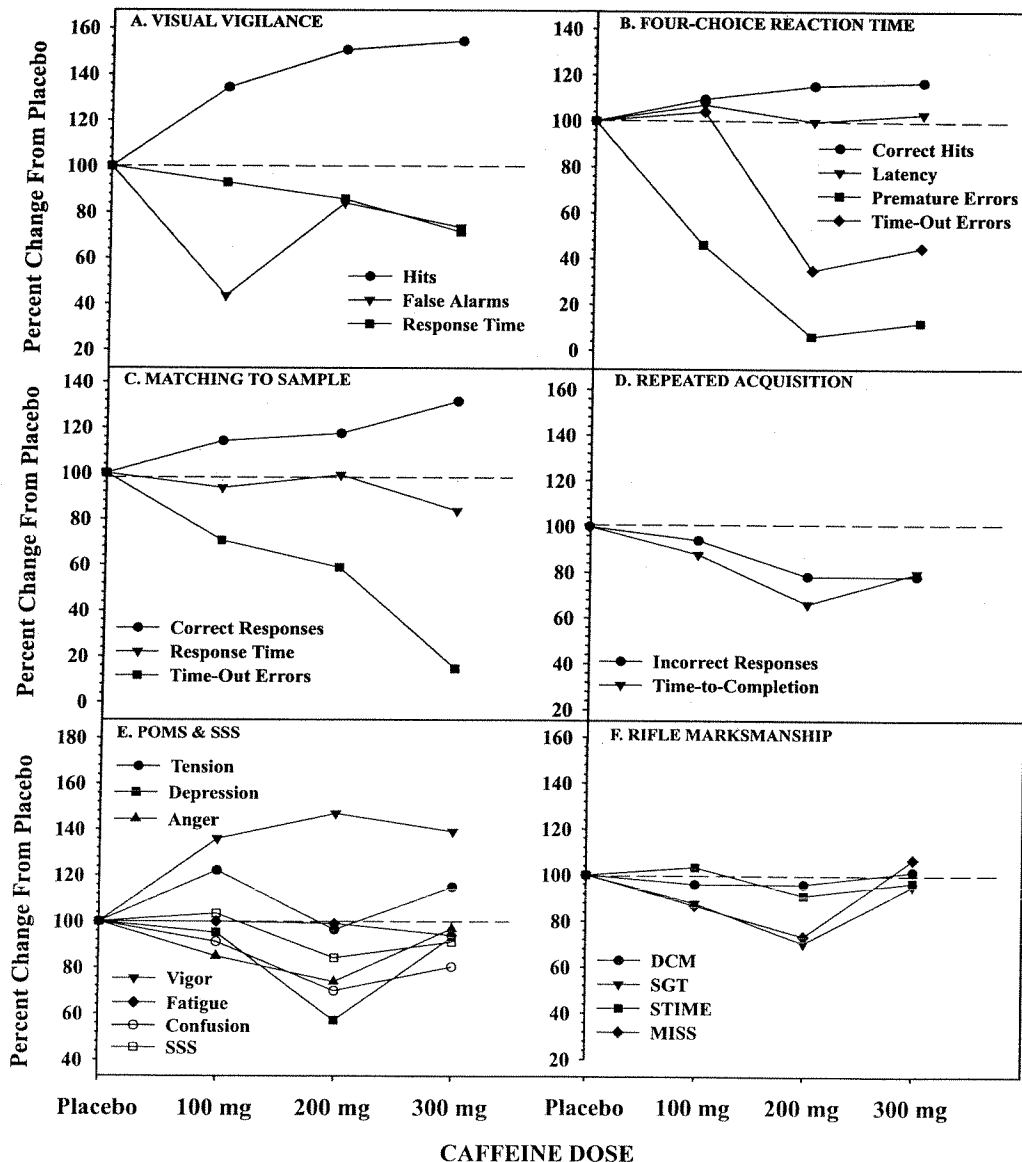


Fig. 3. Percent change in performance and mood following varying doses of caffeine compared to placebo treatment at 1 h post-caffeine administration in a study conducted with severely sleep deprived, environmentally stressed SEAL trainees (Lieberman et al., 2003). (a) Percent change from placebo on measures of visual vigilance. (b) Percent change from placebo on the four choice visual reaction time test. (c) Percent change from placebo on a matching-to-sample test of visual memory. (d) Percent change on a repeated acquisition test, which assesses motor learning and memory. (e) Percent change from placebo on two mood questionnaires, the Profile of Mood States (POMS) and the Stanford Sleepiness Scale (SSS). (f) Percent change from placebo on measures of rifle marksmanship.

it is absorbed more rapidly than caffeine in pill form (Kamimori et al., 2002). This unique formulation may be one of several that could be used in military operations.

In addition to benefits for warfighters engaged in tasks such as sentry duty, monitoring surveillance equipment and conducting sustained operations, caffeine may also have benefits for civilians engaged in similar tasks. For example, several studies have demonstrated that caffeine improves simulated driving performance (Regina, Smith, Keiper, & McKelvey, 1974; Reynier & Horne, 2000).

It has been suggested that caffeine's positive effects will be reduced as users become tolerant to its effects. However, most of the studies reported above were in individuals who were regular users of caffeine, and who were not restricted from caffeine use except immediately prior to testing. In addition, in several studies, where the habitual caffeine use of volunteers has been assessed, there is little or no difference in performance following caffeine administration as a function of prior caffeine consumption history (Fine et al., 1994; Lieberman et al., 1987b).

There are, of course, adverse effects associated with caffeine consumption. Caffeine administration can increase anxiety and unsteadiness, but these effects only seem to occur at doses which are higher than those typically consumed in foods (Lieberman, 1988; Smith, 2002).

In the study conducted with Navy SEAL trainees and discussed above, we found that fine motor control, as assessed by a marksmanship simulator, was actually improved by administration of caffeine at moderate doses (Tharion et al., 1997). Caffeine can also interfere with sleep as reviewed by Smith (2002), so when it is used operationally this must be a consideration. High doses and long acting forms of caffeine are particularly likely to interfere with sleep.

It has been suggested that caffeine has addictive properties (Griffiths, Bigelow, & Liebson, 1986), although this position has been disputed by other scientists (Dews, O'Brien, & Bergman, 2002; Hirsh, 1984). Sudden caffeine withdrawal, particularly among individuals who routinely consume high doses, has been reported to produce adverse effects, such as headache and degraded mood state (Silverman et al., 1992). However, it has been suggested that many of the side-effects of caffeine withdrawal reported in the literature are artifacts related to the expectation of test subjects (Dews et al., 2002). Furthermore, individuals can readily cease using caffeine and not be internally compelled to continue its use, unlike the consequences of using highly addictive drugs such as cocaine and nicotine.

Conclusion

Nutritional neuroscience has only recently begun to coalesce as a separate, identifiable area of scientific inquiry. Military scientists, in part because nutritional interventions

are less controversial and more widely applicable than drugs, have conducted considerable research on the cognitive effects of various nutrients, food constituents and dietary supplements. The greatest progress has been made with regard to caffeine, with an external review panel, the CMNR, recommending it be employed as the 'compound of choice for counteracting cognitive deficits' during military operations (Committee on Military Nutrition Research, Food and Nutrition Board, Institute of Medicine, 2001).

Substantial research with other dietary constituents of value to the military has also been conducted, most notably tyrosine. However, a scientific consensus on the use of this compound has not as yet been achieved. To date, positive findings for tyrosine have been reported from laboratories of all three US military services and also in a European military study. The potentially unique and broad anti-stress properties of this amino acid suggest that further work is warranted. Additional work with macronutrients, especially carbohydrate, and diets that vary in protein to carbohydrate ratio, is also necessary. In general, little work on the effects of dietary constituents in mixed diets has been conducted and their chronic effects on behavior not investigated. Such studies would be of great value, not only to address military requirements, but for the civilian population as well.

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